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TITLE: Metabolizing Enzyme 1 Polymorphisms and Prognosis among Women Treated with Breast Cancer

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This study uses archived tissue and data to examine survival of women treated for breast cancer in relation to inherited polymorphisms of drug metabolizing enzymes. During year 3, we have completed review of over 750 potentially eligible cases and have collected tissue blocks for over 400, so that collection of tissue samples (SOW Task 2) is almost complete. We have obtained updated vital status and cause of death information for eligible subjects. An extension of the project into a fourth year has been approved. Laboratory assays to detect genotypes and tumor markers will be conducted during year 4. No reportable scientific results are available at the end of year 3.

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INTRODUCTION

This study uses archived tissue and data to examine survival of women treated for breast cancer in relation to inherited polymorphisms of drug metabolizing enzymes. We had reported from a pilot study that carrying the homozygous genotype for the glutathione S-transferase (GST)P1 Val^{105} variant, associated with lower enzymes activity toward alkylating agents, or the homozygous genotype for GSTA1*B, a promoter variant that reduces hepatic expression of GSTA1, predicted improved overall among women treated for breast cancer (1, 2). The present, DOD-funded study, extends this area of research to a larger population of women treated for breast cancer and will consider whether these associations are independent of other prognostic markers in tumor tissue. The study design is a retrospective cohort; subject who received first course of therapy for invasive, primary breast cancer at an academic medical center have been identified through the hospital tumor registry. Archived pathological tissue blocks for these women will be the source of tissue for laboratory assays. Genotypes will be determined from normal DNA, and prognostic markers will be evaluated by immunohistochemistry. We will evaluate associations between genotypes and recurrence and overall survival, taking into account other prognostic markers.

BODY

The Statement of Work identified five tasks, as follows:

Task 1. Compilation of Data for Eligible Subjects

Task 2. Archived Tissue Specimens Obtained

Task 3. DNA Extraction and Genotyping

Task 4. Immunohistochemistry

Task 5. Data Analysis and Report Writing

Task 1 was completed during the first year of funding.

Task 2 was initiated during year 2.

During year 3, we have proceeded with Task 2, collecting tissue samples. A total of 771 potentially eligible cases from 3 hospitals were identified by the Fairview University Medical Centers (FUMC) tumor registry have been reviewed by the study coordinator. Of these cases, over 200 could not be included because pathology records and/or tissue could not be obtained (Table 1).

Table 1. Summary of potentially eligible breast cancer cases reviewed

Outcome	Number
Ineligible	
No pathology reports exists in FUMC system	80
In situ disease only	5
No tissue available	
No tissue blocks available	136
Core biopsy tissue only	32
In process	
Requesting slides/blocks	35
Need further review of pathology	23
Completed	
Review complete, blocks obtained	460

For the remaining cases, except for those in process (requesting pathological material) or requiring further review, the study pathologist has reviewed slides and, if the case was eligible on pathological crieria, has selected a normal lymph node block for DNA extraction and a block containing representative tumor tissue for immunohistochemical staining. Tissue sections are have been cut and mounted on slides for over 400 of the cases obtained to date so that material is ready and laboratory assays for Tasks 3 and 4 will start soon.

During year 3 we have obtained updated vital status and cause of death information for eligible subjects through linkage with electronic Minnesota death certificate records.

Unexpected obstacles have been encountered during data collection, resulting in slower progress than what was outlined the original statement of work. A primary problem has been that the proportion of potentially eligible cases with no pathology record in the FUMC system, or no tissue blocks available, is larger than anticipated. Therefore it was not possible to collect samples for an adequate number of study subjects from one hospital as had been originally planned. We expanded the study to several hospitals within the FUMC system in order to accrue a sufficient number of samples. Working with additional hospitals, however, created the necessity of submitting, and waiting for approval of, revisions to IRB the protocols. To work with more hospitals we also needed to hire and train additional part-time personnel. This additional administrative workload on the PI and study coordinator contributed to slower-than-anticipated progress during year 2 and the early part of year 3. Substantial progress has been made during the balance of year 3, and an extension of the project period into year 4 has been approved. At present, in October, 2004, progress on the research has been

slowed while we wait for a response from the DOD IRB to a protocol revision submitted in April, 2004, which included addition of one more FUMC hospital as a source of tissue for the study. If approval of this revision is not received soon, the project will fall further behind schedule and we will not be able to increase the sample size to what was originally planned.

KEY RESEARCH ACCOMPLISHMENTS

Tasks 3, 4, and 5 are yet to be completed. Laboratory assays for genotypes and pathological markers will be underway shortly. No reportable scientific results will be available until these tasks are complete. The PI presented a poster describing study methods and rationale at the "Era of Hope" Department of Defense Breast Cancer Research Program Meeting, Orlando, Florida, September 26-28, 2002.

REPORTABLE OUTCOMES

Abstract

Sweeney C, Gulbahce HE, Coles BF. Metabolizing enzyme polymorphisms and prognosis among women treated for breast cancer. "Era of Hope" Department of Defense Breast Cancer Research Program Meeting, Orlando, FL, September 26-28, 2002.

CONCLUSIONS

Data collection tasks are ongoing, so no reportable scientific results are available to date.

REFERENCES

1. Sweeney C, McClure GY, Fares MY, et al. Association between survival after treatment for breast cancer and glutathione S-transferase P1 Ile105Val polymorphism. Cancer Res 2000;60:5621-5624.

2. Sweeney C, Ambrosone CB, Joseph L, et al. Association between a glutathione S-transferase A1 promoter polymorphism and survival after breast cancer treatment. Int J Cancer 2003;103:810-4.

APPENDICES

N/A